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PATENT
ATTORNEY DOCKET NO.: LEAPS-C11
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
M. Seul

Serial No. 10/645,426

Confirmation No. 8876

Filed: 6/21/2003

For: Arrays Formed of Encoded Beads Having
Ligands Attached

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Group Art Unit: 1641

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Examiner: Do, Pensee T.

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I hereby certify that, on the date indicated below, this
correspondence was sent by fax to the Commissioner
for Patents, at (571) 273 8300.

) By:

Date:

9/15/06

Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

Brief on Appeal

Dear Sir:

Pursuant to the Office Action of 9/11/2006, please review all the rejections in view of the following comments. Please charge the fee of \$250 for the filing of this Brief to Deposit Account No. 502083.

Real Parties in Interest.

The assignee of this application is BioArray Solutions Ltd. of Warren, New Jersey.

Related Appeals and Interferences.

An appeal has also been filed in Serial No. 10/310,173 -- which is a continuation of Serial No. 09/690,040. The present application is also a continuation of Serial No. 09/690,040.

Status of Claims.

Claims 1-75 have been canceled.

Claims 76-92 are pending and have been rejected.

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Status of Amendments

The amendment filed on Mar 16, 2006, has been entered. Although the Office Action of 9/11/2006 was non-final, this application is an RCE, and it was rejected twice before filing of the RCE, and is therefore ripe for appeal. As the same issues and prior art have been repeatedly cited in this case and in related cases, and Applicant's arguments against this prior art have not persuaded the Examiner in this case or in the related cases, it is believed that another response would be futile, and that an appeal is necessary to resolve the impasse.

Summary of Claimed Subject Matter

The claims relates to an array of several different particle-attached ligands, wherein different ligands are attached to different particles and said particles are encoded with a chemical or physical characteristic that permits identification of the ligand or ligands attached thereto and permits distinguishing of particles having different ligands attached thereto from each other, and wherein said particles are in a planar defined area on the surface of a substrate and the particles are affixed to said substrate. The array of particle-attached ligands are intended for use in assays. See specification Example V, page 27 line 31 to page 28, line 5. They are to be reacted with a solution containing (or which may contain) several labeled analytes, each capable of binding to ligand on a differently-encoded particle. Following the binding reaction, the array of particles (distributed on the "planar defined area") is decoded, to identify those particles now associated with a labeled analyte (see specification Example V, page 27 line 31 to page 28, line 5), thus identifying the ligands on such reactive particles, and, in turn identifying individual analytes (which each bind exclusively to particular "ligands"). See specification Example V, page 27, lines 10-20; *see also* specification Example IX, page 45 line 31 to page 46, line 3 -- relating specifically to hybridization assays (claims 79 and

83 specify that the ligand is a "nucleic acid").

Claim 92 states that the "location of each array on said substrate in combination with the chemical or physical characteristic indicates the types of ligands therein." (see page 25, line 5 to page 27 line 6). In this case, there are a plurality of arrays on the substrate (as set forth in claim 91), and the identities of the ligands are "double-encoded," and are decoded by identifying the location of the array in which it is located, and the identity of the encoded bead associated with it.

Grounds of Rejection to Be Reviewed on Appeal

Whether claims 81-83 are indefinite within the meaning of 35 USC § 112, para. 2.

Whether claims 76-84 and 86-90 and 31 are unpatentable under 35 USC § 103(a) over Margel (US 5,652,059) in view of Singer et al. (US 5,573,909).

Whether claim 85 is unpatentable under 35 USC § 103(a) over Margel (US 5,652,059) in view of Singer et al. (US 5,573,909) and further in view of Nacamulli et al. (US 5,527,710)

Whether claims 91 and 92 are unpatentable under 35 USC § 103(a) over Margel (US 5,652,059) in view of Singer et al. (5,573,909) and further in view of Gombinski (US 6,297,062)

Argument

A. Claims 81-83 Are Not Indefinite Within the Meaning of 35 USC § 112, para. 2

The Examiner alleges that in claims 81-83, the terms "proteins" and "oligonucleotides" lack antecedent basis. However, claim 81 depends on claim 78, which recites that the ligands of claim 76 are proteins (the term used in claim 81). Claim 82 depends on claim 78, and recites that the proteins are monoclonal antibodies. Claim 83 (which recites that the "nucleic acids are DNA or RNA") depends on claim 79, which recites that the ligands of claim 76 are nucleic acids. Accordingly, there is proper antecedent basis for the terms in these claims.

The Examiner also alleges that in claims 81 and 83, which recite "an array" there is improper antecedent basis, as it should state "the array." Again, there is proper antecedent basis without making such change.

B. The Subject Matter of Claims 76-84 and 86-90 Is Nonobvious over Margel in View of Singer et al.

The particles in Margel are *not* "encoded." In Example 31 of Margel¹ the: "wells of Eliza (*sic*) titer plates coated with polyacrolein microspheres of 800 Angstrom units average diameter" are incubated with sheep immunoglobulin. Thus, there is only one type of *non-encoded* "polyacrolein microspheres of 800 Angstrom units average diameter ... incubated at room temperature for approximately 15 minutes with 0.1 ml PBS solution containing 0.1 µg sheep immunoglobulins (sIgG)." Accordingly, all the Margel microspheres in Example 31 are coated with the same sIgG and are not "different particles" and are not "encoded with a chemical or physical characteristic that permits identification of the ligand or ligands attached thereto and permits distinguishing of particles having different ligands attached thereto from each other..." as required in claim 76.

Moreover, the particles in Margel Example 31 are not in "a planar defined area on the surface of a substrate ..." as required in claim 76. Margel's particles are coated on the surface of "Eliza (*sic*) titer plates," and such wells are parabolic.

Margel, in fact, does not consider recording assay signals from individual microparticles, and Example 31 teaches away from optical detection of assay signals of

¹ Example 31 is the only (remotely) relevant part of Margel, as Margel is primarily directed to modification of surfaces with microspheres (see first paragraph of Detailed Description, col. 3, lines 20-37):

The present compositions, which incorporate supported microspheres, have many potential applications, for example those already outlined above where the use of microspheres is already known per se. Also, e.g. the present inventive compositions can be used to immobilize drugs, prodrugs, enzymes, proteins, antibodies, biological cells and other controllably releasable substances, merely by way of illustration. It is to be understood that immobilization of any of these materials may be effected by creation of chemical bonds, e.g. covalent, ionic and/or coordinate bonds between reactive functions therein and the residual reactive functions of the supported microspheres. Alternatively or additionally, however, these materials may have merely a physical connection with the supported microsphere compositions, e.g. they may be adsorbed thereon and/or entrapped therein, thus the term "immobilization" is to be understood broadly as denoting chemical bonding and/or physical connection.

individual microparticles immobilized on the substrate surface. Specifically, Example 31 describes the determination of the reactivity of the sheep immunoglobulins with biotinylated antibodies directed against these immunoglobulins by way of reacting the antibodies with Extravidin peroxidase, which produces a detectable chromogenic substance, in accordance with standard ELISA protocols. However, this chromogenic stain diffuses into solution in the well, and cannot be associated with individual microparticles -- and in fact it *hides* individual particles. Rather, an assay signal is recorded from the entire well, not from individual microparticles - for example, by determining optical absorbance.

Singer et al. (5,573,9(9)) relates to "methods for labeling or detecting one or more target materials using surface coated fluorescent microparticles with unique characteristics." See Singer et al. Abstract. Singer et al. discuss microparticle-labeled probes, but the microparticle-labeled probes are not attached "at discrete sites," but rather the targets are *immobilized*, and the microparticles serve only to permit the determination of the presence or absence of immobilized targets. See also col. 4, lines 37-47.

Singer et al. does not disclose the detection of assay signals *and* decoding signatures from such microparticles (decoding would require that particles be distinguishable individually), but only a method of "labeling or detecting one or more target materials" wherein immobilized targets of interest are contacted with probes attached to fluorescently labeled microparticles and then "unbound probes are optionally removed from the sample by conventional methods such as washing." For detection of the target materials, "the *sample is illuminated with means for exciting fluorescence in the microparticle-labeled probes* [see col. 20, line 33, to col. 21, line 36]." Thus, in this part of Singer et al., neither the targets nor the probes are individually encoded, but rather, the presence or absence of fluorescence signals emitted by the microparticle-labeled probes is detected, to indicate the presence or absence of a target decorated with a probe. In other words, if more than one type of particle is present and so illuminated, "smears" of a plurality of different fluorescences can be detected, but different individual particles giving off different fluorescent signals *cannot* be distinguished -- only the different signals can be distinguished. Thus, distinguishing encoded microparticles "having different ligands attached thereto from each other" is not suggested or disclosed

in Singer et al., or in the combination of Margel with Singer et al., and as encoding is not mentioned in either, there is no suggestion of the claimed subject matter.

C. The Subject Matter of Claim 85 Is Nonobvious over Margel in View of Singer et al. and Further in View of Nacamulli et al. (US 5,527,710)

Nacamulli et al. do not disclose or suggest encoded, distinguishable particles. Nacamulli et al. relates to monitoring the reaction of antibody-antigen reaction (between *one type* of reactant and *one type* of reaction partner) by monitoring luminescence intensity. But there is no mention of multiplexed reactions, with reactions of several different types of reactants and reaction partners, as would be required to suggest encoded particles. *See, e.g., Abstract:*

The reaction is conducted in an electrochemical cell with a mixture of reagents including a luminophore which will relate the concentration of a reactant, a reaction partner or the reaction product of a reaction partner to the ECL intensity. The reaction partner is a reagent which reacts with the reactant and which participates with the luminophore (or its reaction product participates with the luminophore) to cause the emission of ECL.

Accordingly, there is no motivation provided by Nacamulli et al., to make encoded, distinguishable particles as set forth in independent claim 76, and accordingly, the rejection of dependent claim 85 should also be reversed.

D. The Subject Matter of Claims 91 and 92 Is Nonobvious over Margel in View of Singer et al. and Further in View of Gombinski (US 6,297,062)

Claim 91 relates to: "two or more of any of the arrays defined in claim 76 to 90 ..." and claim 92 further defines "the location of each array on said substrate in combination with the chemical or physical characteristic indicates the types of ligands therein." Gombinski relates to:

a method for separating at least one species of biological entities from a sample solution, by contacting the sample with a matrix of magnetic particles formed on a substrate such as a sheet a gel, etc. The particles in the matrix are coupled to

entities capable of specifically binding to the species of biological entities to be separated. [see Abstract]

Further, as set forth in the Summary of the Invention (col. 5, lines 38-53) of Gombinski:

Preferably, the matrix should contain magnetic particles, coupled to several different species of second members of the pair forming groups, for example, to different types of antibodies, wherein all the magnetic particles which are coupled to a specific species of said second member are present in a discrete location in the matrix, which is different than the location of the other magnetic particles. When the sample is contacted with said matrix, and each species of biological entities, (first member of the pair forming group, for example, a specific antigen) binds to its specific second member of the pair forming group (for example its specific antibody) *which is present in a discrete location in the matrix. Thus each species of the biological entities is spatially separated, in a discrete location, from the other entities*, and due to the magnetic properties of the magnetic particles, each species may be obtained separately. [emphasis added]

It is clear, however, that the claimed "array of several different particle-attached ligands, wherein *different ligands are attached to different particles* and said particles are encoded with a chemical or physical characteristic *that permits identification of the ligand or ligands attached thereto and permits distinguishing of particles having different ligands attached thereto from each other*" (claim 76; emphasis added) are not present in Gombinski. Gombinski relates to purification by "separating at least one species of biological entities from a sample solution..." (as noted in the Abstract above). Thus, there is no need for encoded particles (as a species is being separated; the assay is not multiplexed), and there is no "teaching" of them, as is clarified by the following passage from Example I (col. 16, lines 34-54):

200 μ l from 1 μ m diameter superparamagnetic *ferrous oxide particles which were coated with a functional affinity group* (Advanced Magnetics, Inc., USA) were drawn from a 50 mg/ml stock solution and were injected to 3 ml of a 2% aqueous solution of low melting point agarose (A-9414, Sigma Chemical Co., USA) at a temperature of 45° C and mixed for 1 minute by a vortex. The agarose was poured into the casting space and then covered with a 7x7 cm hot glass plate. After a few minutes at 35° C. the gel was allowed to cool and was left at room temperature for at least one hour. During this time the magnetic particles were

drawn to the stripped magnet and a stripped matrix of magnetic particles at the bottom layer of the gel was then obtained. The same procedure was repeated with the uniform magnet, whereby a uniformed [sic] matrix of magnetic particles was obtained. [emphasis added]

Accordingly, the Gombinski particles are all coated with the same functional group in order to separate a specific constituent from a sample solution with which the matrix is contacted. If the constituent within the sample binds to the functional group on the particle, the binding event can be detected using a "biological entities-label." But the particles are not encoded with a "physical or chemical characteristic" or otherwise. In contrast to the invention, the particles within a uniform matrix or within a discrete location of the substrate all carry the same functional group - the "biological-entities label" *merely indicates a binding event*. In fact, different species of the Gombinski magnetic particles - precisely because they are not encoded by a physical or chemical characteristic - must be spatially separated, in different discrete locations on the substrate, in order to be identified. This "identification by spatial location" is also shown in Fig. 2, col. 12, lines 15-31 and described in col. 7, lines 16-20, which sections are specifically referenced by the Examiner for support.

Accordingly, as the encoding of the particles in Gombinski is based only on their location in the array, whether or not it is combined with Margel and Singer et al., it cannot disclose or suggest: "the location of each array on said substrate in combination with the chemical or physical characteristic indicates the types of ligands therein," as required in claim 92. In addition, the combination of these references, due to the vast differences in subject matter and encoding methods in each, would not make sense, and thus, the subject matter of claim 91 is also nonobvious because it depends from allowable claim 76 and also for these additional reasons.

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In conclusion, reversal of all rejections is respectfully requested.

Respectfully Submitted,

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Claims Appendix

76. An array of several different particle-attached ligands, wherein different ligands are attached to different particles and said particles are encoded with a chemical or physical characteristic that permits identification of the ligand or ligands attached thereto and permits distinguishing of particles having different ligands attached thereto from each other, and wherein said particles are in a planar defined area on the surface of a substrate and wherein said particles are affixed to said substrate.
77. The array of claim 76 wherein the particles are affixed to the surface of the substrate.
78. The array of claim 76 wherein the ligands are proteins.
79. The array of claim 76 wherein the ligands are nucleic acids.
80. The array of claim 76 wherein, within the planar configuration, the particles are randomly positioned.
81. An array of proteins according to claim 78, wherein different proteins bind to different cell types.
82. The array of proteins according to claim 78, wherein the proteins are monoclonal antibodies.
83. An array of oligonucleotides according to claim 79 wherein the nucleic acids are DNA or RNA.
84. The array according to claim 76, wherein the substrate is a semiconductor.
85. The array according to claim 84 wherein the substrate is an electrode.
86. The array according to claim 76, wherein the chemical or physical characteristic is a chemical tag.
87. The array according to claim 86, wherein the chemical tag can be optically detected.
88. The array according to claim 77, wherein the particles are affixed to the substrate by chemical bonding.
89. The array according to claim 76, wherein the particles are exposed to liquid containing or suspected of containing an analyte.
90. The array according to claim 89, wherein the ligands are nucleic acids capable of hybridizing with one or more analytes contained within the liquid.

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91. An article of manufacture composition comprising two or more of any of the arrays defined in claim 76 to 90.

92. The article of claim 91 wherein the location of each array on said substrate in combination with the chemical or physical characteristic indicates the types of ligands therein.

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Evidence Appendix

None

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Related proceedings Appendix

None

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